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Food and Drug Administration
Public Hearing
Combination Products Containing Live Cellular Components

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INTEGRA® Dermal Regeneration Template

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Objectives:

- Review of INTEGRA® Dermal Regeneration Template - A Skin Replacement System
- Review Current Regulatory Requirements for Product Approval of Skin Replacement Products Under the Center for Devices and Radiological Health (CDRH)
- Recommendations for Data to Support Safety and Effectiveness of Products Intended to be Used for Skin Replacement/Regeneration
- Recommendations for FDA Jurisdiction for Products Intended for Cutaneous Wounds and Burns that Contain Live Cellular Products

Introduction to:
INTEGRA® Dermal Regeneration Template

Indications for Use (USA)

- INTEGRA® Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient
- INTEGRA® Dermal Regeneration Template is also indicated for repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient

INTEGRA® Dermal Regeneration Template

- INTEGRA® is an innovative technology in the wound healing area
- CDRH annual reports have listed INTEGRA® as a significant medical technology breakthrough
- Considered an important technology to have available after the September 11, 2001 terrorist attacks
- Approved on March 1, 1996 and regulated as a Class III Medical Device under the PreMarket Approval Process (PMA P900033)
- Regulated as a Medical Device for 20 years since 1982 when the first Investigational Device Exemption IDE was submitted to FDA
- Regulated as a Medical Device in the European Union, Canada, Japan, Australia and other countries where the product is currently registered (total of over 30 countries)
- INTEGRA® does not contain any live cellular components or recombinant proteins

INTEGRA® Dermal Regeneration Template PMA P 900033

Description:

- A bilayer membrane skin replacement system for the treatment of full-thickness or deep partial-thickness thermal skin injuries and repair of scar contractures
  - Dermal replacement layer
  - Temporary epidermal substitute layer

Dermal Replacement Layer

- There are no live cellular components in INTEGRA® Dermal Regeneration Template
- Three-dimensional porous matrix of cross-linked bovine collagen and glycosaminoglycan (chondroitin-6-sulfate)
- Controlled porosity
- Defined degradation rate
- Promotes cellular ingrowth

Temporary Epidermal Substitute Layer

- Composed of synthetic polysiloxane polymer (silicone)
- Controls moisture loss from wound
- Mechanically protects the wound

Function

- The dermal replacement layer serves as a matrix for the infiltration of fibroblasts and capillaries
- Endogenous collagen matrix is deposited by fibroblasts; simultaneously the dermal layer is degraded
- Upon vascularization of the neodermis, the silicone layer is removed and a thin, meshed epidermal autograft is placed over the "neodermis"
- Cells from the epidermal autograft grow and form a confluent epidermis with a stratum corneum

Critical Functions

- Serves as a template to generate new dermal tissue, "neodermis"
  - Provides immediate physiological wound closure
  - Neodermis is functional dermal tissue and grows with the patient
  - Neodermis readily accepts very thin epidermal autografts

Histology*

- 336 serial biopsies from 131 patients treated with INTEGRA®
- Biopsies obtained 7 days to 2 years after application
- Six sequential phases of repair were discerned
- An intact dermis was achieved with regrowth of apparently normal reticular and papillary dermis
- No scar formation appeared at any time during the course of healing in any of the biopsies of patients examined

*Stern et al, 1990

PreMarket Approval (PMA) Application as a Class III Medical Device - CDRH

- Extensive Safety and Effectiveness Data Submitted to FDA
- Biocompatability Data According to ISO 10993 Including:
  - Cytotoxicity
  - Dermal Irritation
  - Endotoxin Testing
  - Muscle Implant Study
  - Toxicity Studies
  - Acute Systemic Toxicity
  - Subchronic Toxicity
  - Chronic Toxicity
  - Sensitization Studies
  - Pyrogenicity Studies
  - Mutagenicity Studies
- Immunogenicity Studies
- Preclinical Wound Healing Studies

- Multicenter, Controlled, Randomized Clinical Trial at 11 Centers
  - 149 patients, 207 wound sites
  - Histological specimens of wound healing at day 7 up to 2 years
  - Long term follow-up of the patients
- Two Additional Clinical Trials Conducted in Support of the PMA (additional 79 patients, 189 wound sites)
- Postapproval Study - 216 Patients, 841 Wound Sites
- Total 444 Patients, 1237 Wound Sites Evaluated

- Baseline Evaluations
  - Wound site photographs
  - Wound biopsies
  - Wound cultures
  - Laboratory testing
- Test and Control Sites

  Each patient served as their own control
- Acute and Long Term Follow Up
  - Laboratory testing
  - Wound site evaluations
  - Biopsies of the wound site
  - Patient evaluations
  - Investigator evaluations
  - Safety evaluations
  - Patients followed for 12 months
- Immunological Evaluations
- Histology of the wound

Conditions of Approval of INTEGRA® Dermal Regeneration Template

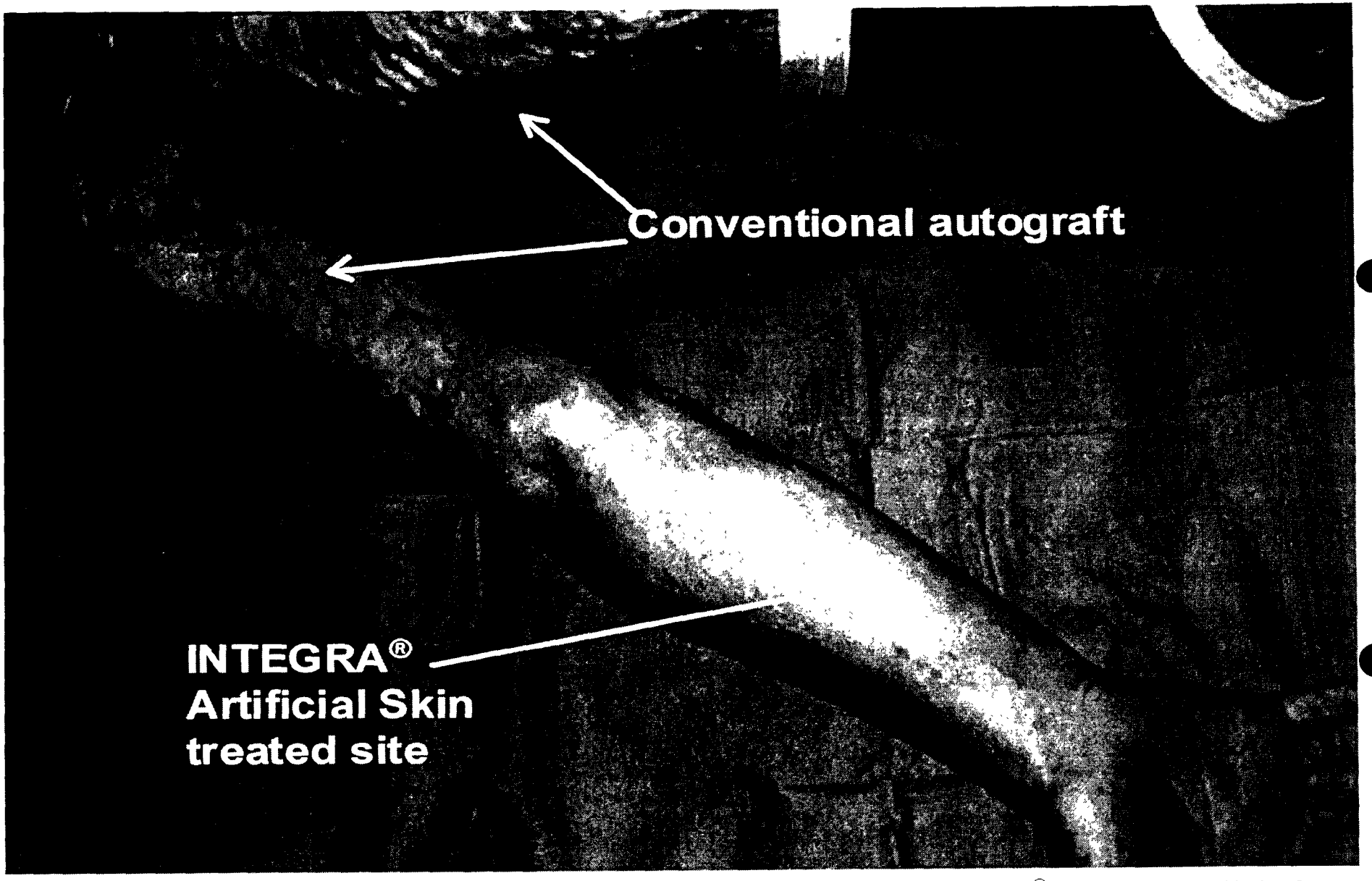
- Postapproval Study - 200 Patients to Collect Additional Information on the Safety and Effectiveness
- Requirement of a Physician Training Program
- FDA Postapproval Requirements
  - Postmarket surveillance
  - Annual reporting to FDA

INTEGRA® - Conditions of Approval (cont.)

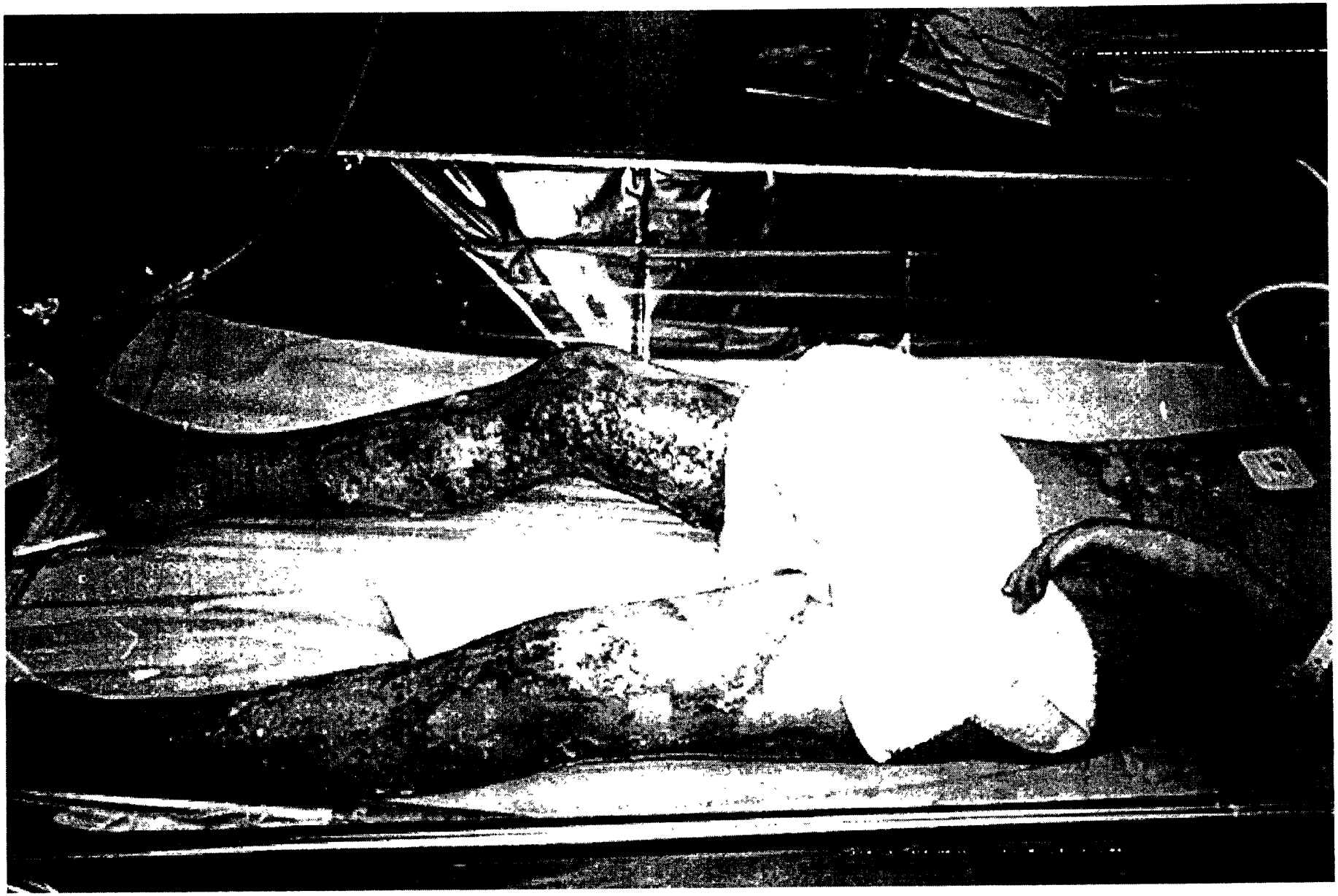
- Restriction on the Sale and Distribution of a Device
- Requirement to Add a Prominent Display of Warnings, Hazards, and Precautions Necessary for Safe and Effective Use to Labeling and to the Advertising of Restricted Devices
- Medical Device Reporting Requirements
- Submission of Annual Reports to FDA

Manufacturing Requirements for INTEGRA® Dermal Regeneration Template

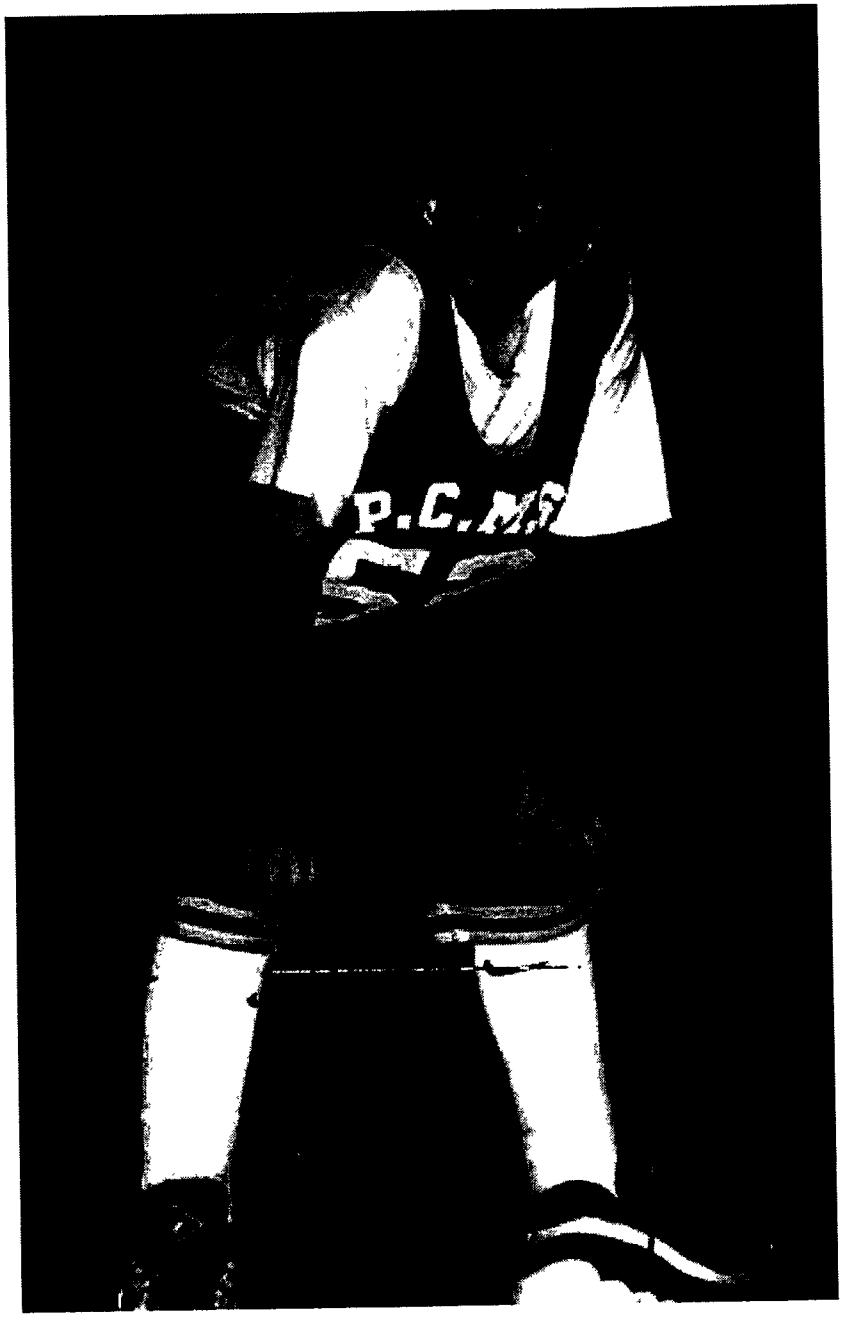
- Product Manufactured in Compliance with FDA Quality System Regulations (Good Manufacturing Practices)
- Facility - FDA Registered; ISO 9001 Certification
- FDA - Pre Approval Inspection and Routine Inspections of the Manufacturing Facility for Compliance with Quality System Regulations
- Annual Reporting to PMA
- PMA Supplements



This Patient was severely burned at age 2 years and treated with INTEGRA® as part of a clinical trial. This is a seven year follow-up.



This is a 12 year old patient with a 40% TBSA deep second and third degree burn that was treated with INTEGRA®.



The patient returned to school in approximately 6 weeks after the initial burn injury and returned to playing sports 4 months after the initial injury. The patient after 3 years has no contractures of the INTEGRA® treated sites and remains active in all sports.

Recommendations for Documents to be Used for Interactive Burn and Wound Dressing Submissions

Premarket Data Can be Addressed through FDA Guidance Documents:

1. FDA Draft Guidance:
   Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment, June, 2000
   Developed by:
   - CDRH - Center for Devices and Radiological Health
   - CBER - Center for Biologics Evaluation and Research
   - CDER - Center for Drug Evaluation and Research
2. FDA Draft Guidance for the Preparation of an IDE Submission for an Interactive Wound and Burn Dressing (April 4, 1995, CDRH)

Data Necessary for Submission

- Standard required information on the company; facility establishment registration
- Reports of prior investigations
  - Data from preclinical studies; clinical trials conducted outside the United States
- Description of the Devices
  - All significant components of the Device
  - Principal of action of each of the Device components

- If Collagen is a component of the dressing:
  - Type of Collagen
  - Tissue and Species
  - Country of Origin
  - Processing of the Collagen
  - Viral Inactivation Study
  - BSE/TSE Risk Analysis

- If Cultured cells are incorporated into the device:
  - Complete description of the origin of the cells
  - Methods of separation from the host tissue
  - Manner in which the cells will be handled and/or pooled
  - Culturing technique
  - Culture media
  - Any agents such as growth factor used in the culturing

- Assurance that the cells are free of transmissible diseases and viruses must be provided
- This should include testing of the donor's blood for $HTLV_{1+2}$, HIV_{1+2}, ALT, Hepatitis B, Hep non A/Hep non B, RPR, and CMV IgM at the time of cell donation
- The test for HIV_{1+2}, should be repeated at six months
- Individual cell strains should be tested for infectious agents, including mycoplasma, sterility, HIV_{1+2}, $HTLV_{1+2}$, HSV_{1+2}, and CMV before pooling
- An in-vitro viral assay should be repeated on the pooled cells before being placed in a Master Cell Bank
- Final product testing should include sterility, mycoplasma, and endotoxin/pyrogenicity tests
- Individual cell lines should be tested to establish the normal human diploid karyotype

- Number of population doublings permitted should be identified
- Quality control procedures used to monitor the cells during the manufacturing process for unusual morphology or growth characteristics must also be described
- If the cells are to be plated onto a substrate, the methods used to monitor cellular viability and density should be described and the minimum levels of acceptability identified
- The validation process should also be described as well as the frequency with which it will be performed

- Biocompatibility Testing
  - Dermal Irritation
  - Dermal Sensitization
  - Cytotoxicity
  - Acute Systemic Toxicity
  - Hemocompatibility/Hemolysis
  - Pyrogenicity
  - Mutagenicity Studies
  - Subchronic Toxicity
  - Chronic Toxicity
  - Carcinogenicity Studies (if indicated)
  - Immunogenic Potential
  - Reproductive/ Developmental Toxicity (if indicated)
  - Absorption Studies
  - ADME Studies (Absorption, Distribution, Metabolism, Excretion) (if indicated)
  - Other Studies Dependent on the Biomaterial being Evaluated

Pre Clinical Testing:

Animal Models for Wounds

- Animal species selected should exhibit a biological responsiveness to the test agent
- No ideal animal model for chronic wound or extensive burns
- Multiple animal models are typically used to assess activity of wound healing agents
- Animal studies selected will depend on the type of wound and claims being sought
- Biodistribution and Pharmacokinetics studies
- Toxicity Studies

Clinical Trial Data

Complete Investigational Plan

- Intended use of the device
- The objectives of the study
- The number of patients to be enrolled and the number of investigational sites that will participate in the study
- The expected duration of the investigation
- A description of the design of the study (e.g. multi-centered, single-blinded, double-blinded, randomized, etc.)
- The inclusion and exclusion criteria which will be used to determine patient eligibility for the study
- The methodology which will be used to assign patients to either the experimental or control groups

The Protocol to be Followed

Pretreatment Regime

- Patient pre-screening for eligibility
- Baseline evaluations such as wound site photographs or measurements
- Wound biopsies or culturing
- Laboratory testing (hematologic, immunologic, urinary)
- Hypersensitivity screening
- Preparation of the wound site (debridement, irrigation, etc.)

The Protocol to be Followed

Treatment Regimen for both the experimental and Control Groups

- Descriptions of both the control and experimental treatments
- The frequency of the treatments
- Other care the patients will receive such as wound debridement/irrigations, dressing changes, laboratory testing, application of topical agents, etc.
- The control treatment must be recognized as the current standard of care for this patient population
- A description of how uniformity of the control and experimental treatments will be maintained across the investigational sites must be provided

The Protocol to be Followed

Post-Treatment Regimen

- Description of the follow-up schedule must be provided
- Frequency of the follow-up visits as well as a description of treatment
  - All laboratory testing
  - Dressing changes
  - Wound site evaluations such as photographs and tracings/molds
  - Biopsies of wound sites for histological evaluations

Wound Assessment

Device Effectiveness Evaluation

- The study endpoints must be clearly identified
- The rationale for the selection of these endpoints
- The parameters used to evaluate the effectiveness of the dressing in the management of the indicated wound
- Comparison to Standard Care

Wound Assessment

Device Effectiveness Evaluation

- Wound Healing Measurements
  - Validated scales
    Example: Vancouver Burn Scar Assessment
  - Histology of the tissue repaired
  - Time to wound healing
  - Long term follow up
  - Evaluation of cosmetic outcome
  - Patient and investigator evaluations
  - Scar assessment evaluated by a panel of masked evaluators
  - Standardized photographs pre and post treatment
  - Photographs evaluated by a panel of masked evaluators
  - Patient satisfaction/quality of life scale using a validated measurement tool

Postapproval Requirements

- Postapproval Study or Postmarket Surveillance Study if indicated to collect additional information about the safety, effectiveness and reliability of the device
- Restriction on the sale and distribution of a device because of a high risk of harm or the need for collateral measures to ensure safe and effective use
- Requirement to add a prominent display of warnings, hazards, and precautions necessary for safe and effective use of labeling and to the advertising of restricted devices
- Requirement to include identification codes on the device, in its labeling or on cards given to patients with implants, if necessary to protect public health (if indicated)
- Requirement to maintain device tracking records in order to trace patients, if it becomes necessary to protect public health (if indicated)

Postapproval Requirements

- Submission of periodic reports (Annual Reports) containing information pertaining to:
  - Change in the device that could affect its safety and effectiveness
  - Changes that do not affect safety and effectiveness
  - Summary and bibliography of information not previously submitted including reasonably known published and unpublished reports of data from any nonclinical or clinical study involving the device or related devices
- Requirement to provide FDA with continued reasonable assurance of the safety and effectiveness of the device
- Physician training program if indicated
- Other postapproval requirements as indicated and necessary to assure the safety and effectiveness of the device

Conclusion

- The FDA Guidance for Industry - Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment, developed by FDA - CBER, CDRH and CDER, provides the framework for developing these products and should be finalized and implemented
- Products for skin replacement/regeneration, chronic cutaneous ulcers could remain in the Center for Devices with consultation from CBER or CDER depending on the components
- The Center for Devices has the technological experience with evaluating these submissions for skin replacement/regeneration

Conclusion

- INTEGRA® Dermal Regeneration Template contains no live cellular components
- INTEGRA® Dermal Regeneration Template has been regulated as a Class III Medical Device for 20 years
- The review of INTEGRA® by CDRH has been rigorous
- There are no current public health concerns with INTEGRA®
- INTEGRA® has been evaluated since 1982 and marketed for 6 years with an adverse event rate of < 0.02%
- INTEGRA® Dermal Regeneration Template has demonstrated extensive safety and effectiveness data and long term safety and effectiveness data
- CDRH has provided extensive review of burn and interactive wound dressing products and it should continue to be the primary reviewers of these products